

What is claimed is:

1. An isolated nucleic acid molecule having the sequence of SEQ ID NO:1, said nucleic acid molecule comprising a nucleotide sequence encoding a MOAT-B transporter protein about 1350 amino acids in length, said encoded transporter protein comprising a multi-domain structure including a tandem repeat of nucleotide binding folds appended C-terminal to a hydrophobic domain, said nucleotide binding folds having Walker A and B ATP binding sites, said C-terminal domain having a plurality of membrane spanning helices.
2. The nucleic acid molecule of claim 1, which is DNA.
3. The DNA molecule of claim 2, which is a cDNA comprising a sequence approximately 5.9 kilobase pairs in length that encodes said MOAT-B transporter protein.
- ~~4. The DNA molecule of claim 2, which is a gene comprising introns and exons, the exons of said gene specifically hybridizing with the nucleic acid of SEQ ID NO 1, and said exons encoding said MOAT-B transporter protein.~~
5. An isolated RNA molecule transcribed from the nucleic acid of claim 1.
- ~~6. The nucleic acid molecule of claim 1, wherein said sequence encodes a MOAT-B transporter~~

protein having an amino acid sequence selected from the group consisting of SEQ ID NO 2 and amino acid sequences encoded by natural allelic variants of said sequence.

7. The nucleic acid molecule of claim 6, which comprises SEQ ID NO 1.

8. An antibody immunologically specific for the protein encoded by the nucleic acid of claim 1.

9. An antibody as claimed in claim 8, said antibody being monoclonal.

10. An antibody as claimed in claim 8, said antibody being polyclonal.

11. An isolated nucleic acid molecule having the sequence of SEQ ID NO: 3, said nucleic acid molecule comprising a sequence encoding a MOAT-C transporter protein about 1450 amino acids in length, said transporter protein having a multi-domain structure including a tandem repeat of nucleotide binding folds, said nucleotide binding folds having Walker A and B binding sites, and a C-terminal hydrophobic domain that contains several membrane spanning helices.

12. The nucleic acid molecule of claim 11, which is DNA.

13. The DNA molecule of claim 12, which is a cDNA comprising a sequence approximately 6.6 kilobase pairs in length that encodes said MOAT-C transporter protein.

14. The DNA molecule of claim 12, which is a gene comprising introns and exons, the exons of said gene specifically hybridizing with the nucleic acid of SEQ ID NO 3, and said exons encoding said MOAT-C transporter protein.
15. An isolated RNA molecule transcribed from the nucleic acid of claim 11.
16. The nucleic acid molecule of claim 11, wherein said sequence encodes a MOAT-C transporter protein having an amino acid sequence selected from the group consisting of SEQ ID NO 4 and amino acid sequences encoded by natural allelic variants of said sequence.
17. The nucleic acid molecule of claim 11, which comprises SEQ ID NO 3.
18. An antibody immunologically specific for the protein encoded by the nucleic acid of claim 11.
19. An antibody as claimed in claim 18, said antibody being monoclonal.
20. An antibody as claimed in claim 18, said antibody being polyclonal.
21. An oligonucleotide between about 10 and about 200 nucleotides in length, which specifically hybridizes with a protein translation initiation site in a nucleotide sequence encoding amino acids of SEQ ID NO 4.

22. An oligonucleotide between about 10 and about 200 nucleotides in length, which specifically hybridizes with a protein translation initiation site in a nucleotide sequence encoding amino acids of SEQ ID NO 2.

23. An isolated nucleic acid molecule having the sequence of SEQ ID NO: 5, said nucleic acid molecule comprising a sequence encoding a MOAT-D transporter protein about 1550 amino acids in length, said transporter protein having a multi-domain structure including a tandem repeat of nucleotide binding folds, said nucleotide binding folds having Walker A and B binding sites, and a C-terminal hydrophobic domain that contains several membrane spanning helices.

24. The nucleic acid molecule of claim 23, which is DNA.

25. The DNA molecule of claim 24, which is a cDNA comprising a sequence approximately 6 kilobase pairs in length that encodes said MOAT-D transporter protein.

26. The DNA molecule of claim 24, which is a gene comprising introns and exons, the exons of said gene specifically hybridizing with the nucleic acid of SEQ ID NO 5, and said exons encoding said MOAT-D transporter protein.

27. An isolated RNA molecule transcribed from the nucleic acid of claim 23.

28. The nucleic acid molecule of claim 23, wherein

WO 99/49735

PCT/US99/06644

said sequence encodes a MOAT-D transporter protein having an amino acid sequence selected from the group consisting of SEQ ID NO 6 and amino acid sequences encoded by natural allelic variants of said sequence.

29. The nucleic acid molecule of claim 23, which comprises SEQ ID NO 5.

30. An antibody immunologically specific for the protein encoded by the nucleic acid of claim 23.

31. An antibody as claimed in claim 30, said antibody being monoclonal.

32. An antibody as claimed in claim 30, said antibody being polyclonal.

33. An oligonucleotide between about 10 and about 200 nucleotides in length, which specifically hybridizes with a protein translation initiation site in a nucleotide sequence encoding amino acids of SEQ ID NO 6.

34. An isolated nucleic acid molecule having the sequence of SEQ ID NO:7, said nucleic acid molecule comprising a nucleotide sequence encoding a MOAT-E transporter protein about 1503 amino acids in length, said transporter protein having a multi-domain structure including a tandem repeat of nucleotide binding folds, said nucleotide binding folds having Walker A and B binding sites, and a C-terminal hydrophobic domain that contains several membrane spanning helices.

35. The nucleic acid molecule of claim 34,

WO 99/49735

PCT/US99/06644

which is DNA.

36. The DNA molecule of claim 35, which is a cDNA comprising a sequence approximately 6 kilobase pairs in length that encodes said MOAT-E transporter protein.

37. The DNA molecule of claim 35, which is a gene comprising introns and exons, the exons of said gene specifically hybridizing with the nucleic acid of SEQ ID NO 7, and said exons encoding said MOAT-E transporter protein.

38. An isolated RNA molecule transcribed from the nucleic acid of claim 34.

39. The nucleic acid molecule of claim 34, wherein said sequence encodes a MOAT-E transporter protein having an amino acid sequence selected from the group consisting of SEQ ID NO 8 and amino acid sequences encoded by natural allelic variants of said sequence.

40. The nucleic acid molecule of claim 39, which comprises SEQ ID NO 7.

41. An antibody immunologically specific for the protein encoded by the nucleic acid of claim 34.

42. An antibody as claimed in claim 41, said antibody being monoclonal.

43. An antibody as claimed in claim 41, said antibody being polyclonal.

WO 99/49735

PCT/US99/06644

44. An oligonucleotide between about 10 and about 200 nucleotides in length, which specifically hybridizes with a protein translation initiation site in a nucleotide sequence encoding amino acids of SEQ ID NO 7.

has > 45. A plasmid comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 and SEQ ID NO:7.

46. A vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 and SEQ ID NO:7.

47. A retroviral vector comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 and SEQ ID NO:7.

48. A host cell comprising at least one nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 and SEQ ID NO:7.

49. A host cell as claimed in claim 48, wherein said host cell is selected from the group consisting of bacterial, fungal, mammalian, insect and plant cells.

50. A host cell as claimed in claim 48, wherein said nucleic acid is provided in a plasmid and is operably linked to mammalian regulatory elements which confer high expression and stability of mRNA transcribed from said nucleic acid.

51. A host cell as claimed in claim 48, wherein said nucleic acid is provided in a plasmid and is operably linked to mammalian regulatory control elements in reverse anti-sense orientation.

52. A host animal comprising at least one nucleic acid molecule selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 and SEQ ID NO: 7.

53. A host animal as claimed in claim 52, wherein said animal harbors a homozygous null mutation in its endogenous MOAT gene wherein said mutation has been introduced into said mouse or an ancestor of said mouse via homologous recombination in embryonic stem cells, and further wherein said mouse does not express a functional mouse MOAT protein.

54. The transgenic mouse of claim 53, wherein said mouse is fertile and transmits said null mutation to its offspring.

55. The transgenic mouse of claim 53, wherein said null mutation has been introduced into an ancestor of said mouse at an embryonic stage following microinjection of embryonic stem cells into a mouse blastocyst.

Ans 98 56. A method for screening a test compound for inhibition of MOAT mediated transport, comprising:

a) providing a host cell expressing at least one MOAT-encoding nucleic acid having a sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, and 7;

WO 99/49735

PCT/US99/06644

b) contacting said host cell with a compound suspected of inhibiting MOAT-mediated transporter activity; and

c) assessing inhibition of transport mediated by said compound.

57. A method as claimed in claim 56, wherein inhibition of MOAT mediated transport is indicated by restoration of anticancer drug sensitivity.

58. A method as claimed in claim 57, wherein said inhibition of MOAT mediated transport is indicated by a reduction of transporter mediated cellular efflux of anticancer agents.

59. A kit for detecting the presence of MOAT encoding nucleic acids in a sample, comprising:

- a) oligonucleotide primers specific for amplification of MOAT encoding nucleic acids;
- b) polymerase enzyme;
- c) amplification buffer; and
- d) MOAT specific DNA for use as a positive control.

*and
Abstract
p. 2*